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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,006	12/03/2003	Rodney Martin Sambrook	S1011/20168 (case 277A)	7204

3000 7590 12/27/2006

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EXAMINER	
SCHLIENTZ, LEAH H	
ART UNIT	**PAPER NUMBER**
1618	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/27/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,006	SAMBROOK ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-74* is/are pending in the application.

4a) Of the above claim(s) *46-48,50,66-71 and 74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-45, 49, 51-65, 72, and 73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/362,314.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply mailed on 11/13/2006 is acknowledged. Applicant's traversal was on the grounds that the claims are all drawn to a porous ceramic carrier and a second material, and that the general chemical, resin, petroleum derivative, or explosive of Group II constitutes a second material. This is not found to be persuasive because while the statement defining Group I does not specifically state that the second material of Group I is a pharmaceutical, it was explicitly stated as such in the description of distinctness between Groups I and II, where the second materials in Group I are pharmaceuticals which are useful *in vivo*, and which have a different mode of operation than those of Group II which include explosives, etc., and are not intended for biological use. Because of the divergent subject matter and classification, undue burden of search has been demonstrated, and the restriction is maintained. The election of the chemotherapeutic agent species, specifically MTX, is also acknowledged. Claims 38 - 74 are pending. Claims 46 – 48, 50, 66 – 71 and 74 have been withdrawn from consideration as being drawn to non-elected species.

Specification

The disclosure is objected to because of the following informalities: the limitations of claims 38, 40, and 41, wherein the pores are in the range of about 20 to about 800 micron, or about 60 to about 800 micron, are not specifically recited in the specification

as originally filed. Also, the limitation of claim 44 wherein the density ranges from about 10% to about 30% of theoretical density is not specifically recited in the specification as originally filed. Appropriate correction is required.

Claim Objections

Claim 38 is objected to because of the following informalities: the claim contains a typographical error wherein "Interconnected" appears, rather than "interconnected." Appropriate correction is required.

Claim 55 is objected to because of the following informalities: the claim appears to be a Markush-type claim, but the support materials are not listed in the alternative. It appears that the term "or" was omitted from the claim before PPA. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 45 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "or the like" renders the claim(s) indefinite because the claim(s) include elements not actually disclosed (those encompassed by "or the like"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

Claim 55 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim contains abbreviations which represent various polymers, including PCPP.SA, PCC, CPP.SA, FAD-SAPTMC, PAA. However, except for PCPP.SA (i.e. (poly(carboxy phenoxy)propane-sebacic acid), the specification does not define the chemical identity of the abbreviations for these polymers (especially PCC, FAD-SAPTMC, and PAA). The claim is unclear regarding the identity of the polymers, especially because some of the abbreviations are ambiguous. For example, PAA is known to represent polyacrylic acid, polyaspartic acid, or possibly additional polymers.

Claim 58 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "high enough" in the claim is a relative term which renders the claim indefinite. The term "high enough" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Specifically, it is unclear regarding the specific physically measurable degree of reticulation that the carrier should demonstrate in order to reduce the pressure gradient generated by infiltration of the second material into the pores therein, especially when the specific pressure gradient is also unspecified in the claim or specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 38 – 45, 49, 58, 59, 61, 62, 64, 65, 72, and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Itokazu *et al.* (*J. Biomed. Mater. Res.*, 1998, 39, p. 536 – 538).

Itokazu teaches porous apatite ceramics (PAC), including β-tricalcium phosphate (TCP), which have a porosity of 75 – 80% and pore size range of 100 – 400 μm for the sustained release of a chemotherapeutic, methotrexate (MTX) (abstract). It is noted that a ceramic with a porosity of 75 – 80% would inherently have a theoretical density of 20 – 25%. The MTX was loaded into the pores of the ceramic carrier via centrifugation (page 536). The TCP is resorbable (page 538).

With regard to the limitations of claims 39 and 58, wherein the skeleton of the ceramic is made up of scaffolding and struts and has a degree of reticulation high enough to reduce the pressure gradient generated in infiltration of the second material into the pores of the carrier, it is interpreted that the porous ceramic of Itokazu would

inherently meet these limitation because the ceramic is materially the same as that which is instantly claimed, and thus would have the same properties.

Regarding claim 42, the limitation wherein "the micropores were formed by sintering the precursor of the carrier under conditions which were below those required for full sintering" appears to be a product-by-process type limitation. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." See *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

The limitations of claims 72 and 73, wherein the ceramic carrier is shaped for orthopaedic maxillo-facial, or cranio-facial replacement or is shaped for location at an intramuscular site, subcutaneous site, etc., appear to be intended use-type limitations, because there are no limitations regarding the actual physical shape of the carrier. Itokazu teaches his MTX-impregnated apatite ceramic devices for local chemotherapy, in treating microscopic diseased bone after curettage (page 538).

Claims 38 – 44, 51, 52, 61, 63, 72, and 73 are rejected under 35 U.S.C. 102(e) as being anticipated by Imura *et al.* (US 6,340,648).

Imura teaches a calcium phosphate porous sintered body which comprises spherical pores communicating with one another substantially throughout the body, and with a porosity between 55 – 90% (i.e. a theoretical density of 10 – 45%) (abstract). The pore diameter is preferably 200 – 5000 μm (column 4, line 5). The device may be a carrier for drug delivery and gradual release (column 1, lines 5 – 10), and medicine for promoting osteogenesis (or another medicament) may be included within the pores (column 6, lines 63 – 67). The surface of the material is etched with acid by dipping the porous sintered body into acid and passing the acid into the pores, which results in remarkable etching of the surface of the body and uniform etching of the inner part of the calcium phosphate porous sintered body (column 6, lines 4 – 15). The ceramic material is calcium phosphate, and may be calcium phosphate hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$ (column 4, lines 46 – 50 and claim 3).

Regarding the limitation of claims 39, wherein the skeleton of the ceramic is made up of scaffolding and struts, it is interpreted that the porous ceramic of Imura would inherently meet this limitation because the ceramic is materially the same as that which is instantly claimed, and thus would have the same properties.

The limitations of claims 72 and 73, wherein the ceramic carrier is shaped for orthopaedic maxillo-facial, or cranio-facial replacement or is shaped for location at an intramuscular site, subcutaneous site, etc., appear to be intended use-type limitations, because there are no limitations regarding the actual physical shape of the carrier. Imura teaches his ceramic devices for a substitute for repairing material for bone or

tooth, a carrier for material for drug delivery and gradual release, and an induction vessel for bone, etc. (column 1, lines 5 – 10).

Claims 38 – 45, 59 – 61, 72, and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Hakamatsuka *et al.* (US 5,318,779).

Hakamatsuka teaches a drug-impregnated ceramic to be embedded in a living body. The porous ceramic has pores with a size of 10 – 300 μm, a drug impregnating the ceramic pores, and a surface layer for controlling the release of the drug (abstract). The porous ceramic is formed of tricalcium phosphate (TCP), which is adsorbed by a living body (column 2, lines 45 – 50). The porosity of the ceramic may be 70% (i.e. the ceramic may have a density of 30% of theoretical) (Table 1, Example 3). The surface layer consists of collagen having a 10 μm pore size and a thickness of 300 μm (i.e. a biodegradable polymer) (claim 7). An antibiotic was impregnated within the ceramic by dipping the entire ceramic capsule into antibiotic solution (column 4, lines 50 – 60). While it is not explicitly stated that the drug is contained in the collagen polymer, it is interpreted that at least a portion of the drug would be contained in the pores of the collagen polymer as the capsule was dipped into the solution containing the drug.

Regarding the limitation of claims 39, wherein the skeleton of the ceramic is made up of scaffolding and struts, it is interpreted that the porous ceramic of Hakamatsuka would inherently meet this limitation because the ceramic is materially the same as that which is instantly claimed, and thus would have the same properties.

With regard to claim 42, the limitation wherein "the micropores were formed by sintering the precursor of the carrier under conditions which were below those required for full sintering" appears to be a product-by-process type limitation. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." See *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

The limitations of claims 72 and 73, wherein the ceramic carrier is shaped for orthopaedic maxillo-facial, or cranio-facial replacement or is shaped for location at an intramuscular site, subcutaneous site, etc., appear to be intended use-type limitations, because there are no limitations regarding the actual physical shape of the carrier. Hakamatsuka teaches his ceramic devices to be embedded in an affected region of a living body in order to treat myelitis, malignant tumor, etc. (column 1, lines 9 – 12).

Claims 38 – 44, 53, 54, 61 – 63, 72, and 73 are rejected under 35 U.S.C. 102(e) as being anticipated by Starling *et al.* (US 6,358,532).

Starling discloses calcium phosphate-based microcarriers and their use as implantable biomedical materials (abstract). The calcium phosphate may be

hydroxyapatite, tricalcium phosphate, etc. (column 6, line 8). The density of the microcarrier may be from 25 – 75% of theoretical density. The pore size is from 30 – 80 μm (column 6, lines 15 – 22). A calcium phosphate microcarrier with open porosity can be used with collagen to form a composite implantable material. The open porosity within the microsphere is made by sintering at a temperature less than that required to fully densify the material. The open porosity can be adjusted to deliver pharmaceutical agents. The pharmaceutical agents (i.e. a second material) are impregnated within the pores of the microcarrier (column 9, lines 10 – 35).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 38 – 45, 49, 58, 59, 61 – 65, 72, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Itokazu *et al.* (*J. Biomed. Mater. Res.*, 1998, 39, p. 536 – 538).

Itokazu teaches porous apatite ceramics (PAC), including β-tricalcium phosphate, which have a porosity of 75 – 80% (i.e. a theoretical density of 20 – 25%) and pore size range of 100 – 400 μm for the sustained release of a chemotherapeutic, methotrexate (MTX) as set forth above. Another porous apatite ceramic which is taught by Itokazu is calcium phosphate hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), or HAb, which has a porosity of 35 – 48% (i.e. a theoretical density of 52 – 65%) and pore size of 50 – 300 μm (page 536).

The calcium phosphate hydroxyapatite ceramic taught by Itokazu does not have a theoretical density of less than 40% theoretical.

It would have been obvious to one of ordinary skill in the art to utilize a calcium phosphate hydroxyapatite sample with a lower theoretical density (i.e. including less than 40% theoretical), similar to a theoretical density between 20 – 25% for the TCP

sample also taught by Itokazu, because the TCP released higher concentrations of MTX at a slower rate than the HAb, which was attributed to the higher porosity (or lower theoretical density) and larger pore size. The HAb showed a higher mechanical strength (page 538). Both tricalcium phosphate and calcium phosphate hydroxyapatite ceramics have been employed as porous devices for drug delivery. One would have been motivated to adjust the adjust the porosity of samples of calcium phosphate hydroxyapatite to be similar to that of the TCP employed in the experiments of Itokazu (i.e. including less than 40% theoretical) in order to achieve a carrier with an optimal balance of a desirable MTX release profile and adequate mechanical strength.

Claims 38 – 45, 49, 53, 54, 56 – 59, 61 – 65, 72, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Genin (US 6,767,550) in view of Itokazu *et al.* (*J. Biomed. Mater. Res.*, 1998, 39, p. 536 – 538).

Genin teaches a hydroxyapatite based drug delivery implant for cancer treatment. Sustained release of the anti-cancer agents may be achieved after implantation at targeted sites (abstract). The ceramic component of the implant may be tricalcium phosphate, hydroxyapatite, etc. (column 2, lines 51 – 57). The implant has two layers, a first layer consisting of pure hydroxyapatite and the second layer contains hydroxyapatite, a bioresorbable material (i.e. collagen or polymer), and doxorubicin (an anti-cancer agent) (claim 1). The first layer may further comprise polymer or collagen (claim 4). The implant may be porous (claim 6). When the implant is porous, the pore size is between 1 μm – 3 mm, depending on the desired drug release profile (column 6,

lines 35 – 40). Thus, Genin teaches a carrier which has an alternating agent-free layer and an agent-containing layer (i.e. the layers are different from the neighboring layer).

Genin fails to identify the specific density of the ceramic used in his porous ceramic implant. Thus, he does not teach that his anti-cancer drug delivery device has a density which is specifically less than 40% theoretical.

Itokazu teaches porous apatite ceramics (PAC), including β-tricalcium phosphate and hydroxyapatite, which may have a porosity of 75 – 80% (i.e. a theoretical density of 20 – 25%) and pore size range of 100 – 400 μm for the sustained release of a chemotherapeutic agent as set forth above.

Itokazu does not teach that the porous apatite ceramics further comprise a biodegradable support (i.e. collagen or polymer), and that the pores contain layers of chemotherapeutic agent and biodegradable support, each layer being different from its neighbors, as in alternating layers of agent-free layers and agent-containing layers.

It would have been obvious to one of ordinary skill in the art to utilize a ceramic with a density of less than 40% theoretical in the drug delivery implant of Genin consisting of drug-containing and drug-free layers because Itokazu demonstrated successful modified release of an anticancer agent via a similar ceramic with a theoretical density of 20 – 25%. Itokazu identified porosity/density as a key factor in controlling release of an anticancer drug from a ceramic (page 538). One would have been motivated to do so in preparing a ceramic with a desired release profile, because Genin specifically teaches that modification of the microstructure, morphology, and composition of the bioresorbable material (i.e. ceramic or polymer) allows for control of

the drug release profile (abstract). Genin also teaches that his implants may be dense or porous and refers to tailoring the pore size in the porous implants depending on the desired drug release profile (column 6, lines 35 – 40).

Claims 38 – 45, 49, 53 – 55, 58, 59, 61 – 64, 72, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bohner *et al.* (*J. Pharm. Sci.*, 1997, 86, p. 565 – 572) in view of Itokazu *et al.* (*J. Biomed. Mater. Res.*, 1998, 39, p. 536 – 538).

Bohner teaches calcium phosphate cement of tricalcium phosphate and monocalcium phosphate hydrate as a delivery system for the antibiotic gentamicin sulfate (abstract). The calcium phosphate carrier may have a porosity of 70% (i.e. a density of 30% theoretical) (Figure 7). Polyacrylic acid was added to the carrier as a release-modifier (page 565).

Bohner fails to identify the size of the pores within the calcium phosphate. Thus, he does not teach that his drug delivery device has pores which are in the range of 20 – 800 micron.

It would have been obvious to one of ordinary skill in the art to use a calcium triphosphate ceramic with pores which are in the range of 20 – 800 micron in the calcium phosphate/PAA drug delivery device taught by Bohner because Itokazu teaches a similar calcium phosphate material having similar porosity (i.e. 75%) and a pore size of 100 – 400 μm to be an effective sustained-release drug delivery device for implantation into bone. One would have been motivated to do so to obtain a carrier with a desired drug release profile. One would have had a reasonable expectation of

success in doing so because both the ceramic calcium phosphate having a porosity of 75% with 100 – 400 μm pores and the calcium phosphate cement having porosity of 70% in combination with PAA were shown to act as delivery systems for the sustained release of pharmaceuticals in bone, including antibiotics and chemotherapeutic agents.

Conclusions

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER